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The Effect of Short-Term Low-Dose Perchlorate on Various Aspects of Thyroid Function

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Perchlorate (ClO_4) salts are found in rocket fuel, fireworks, and fertilizer. Because of ground water contamination, ClO_4 has recently been detected in large public water supplies in several states in the 4–18 $\mu g/L$ (parts per billion [ppb]) range. The potential adverse effect of chronic low level ClO_4 ingestion on thyroid function is of concern to the Environmental Protection Agency (EPA). The daily ingestion of ClO_4 at these levels would be magnitudes below the therapeutic effect level of hundreds of milligrams of ClO_4 used in treating hyperthyroidism. Studies were carried out in nine healthy male volunteers who had normal thyroid function and negative thyroid antibodies to determine whether the ingestion of 10 mg of ClO_4 daily (approximately 300 times the estimated maximum amount of ClO_4 consumed from the affected water supplies) would affect any aspect of thyroid function. They ingested 10 mg of ClO_4 dissolved in a liter of spring water during waking hours for 14 days. Baseline serum thyrotropin (TSH), free thyroxine index (FTI), total triiodothyronine (TT_3), 4-, 8-, and 24-hour thyroid ^{123}I uptakes (RAIU), serum and 24-hour urine ClO_4, 24-hour urine iodine, complete blood count (CBC), and chemistry profile were determined. All blood and urine tests were repeated on days 7 and 14 of ClO_4 administration and thyroid RAIU on day 14 of ClO_4 administration. All tests were repeated 14 days after ClO_4 was discontinued. No effect of ClO_4 on serum thyroid hormone or TSH concentrations, urinary iodine excretion, CBC, or blood chemistry was observed. Urine and serum ClO_4 levels were appropriately elevated during the course of ClO_4 ingestion in all subjects, demonstrating compliance. By day 14 of ClO_4 administration, the 4-, 8-, and 24-hour thyroid RAIU values decreased in all nine subjects by a mean value of 38% from baseline and rebounded above baseline values by 25% at 14 days after ClO_4 withdrawal ($p < 0.01$ analysis of variance (ANOVA) and Tukey). It is well known that the major effect of ClO_4 on the thyroid is a decrease in the thyroid iodide trap by competitive inhibition of the sodium iodide symporter (NIS). The present study demonstrates the sensitivity of the thyroid iodide trap to ClO_4 because a low dose of 10 mg daily significantly decreased the thyroid RAIU without affecting circulating thyroid hormone or TSH concentrations. It is possible, however, that the daily consumption of low levels of ClO_4 in drinking water over a prolonged period of time could adversely affect thyroid function but no evidence of hypothyroidism was observed at 10 mg of ClO_4 daily in this 2-week study. It is now of interest to determine a no effect level for ClO_4 on the inhibition of the thyroid RAIU and to carry out a long-term ClO_4 exposure study.

Introduction

PERCHLORATES HAVE BEEN USED for more than 50 years as oxidizers in solid propellants for rockets and missiles in the space program. In addition, perchlorates have been used in fireworks, and more recently, in road flares and air bag inflation systems and have been found in some commercial fertilizers. Perchlorate salts are highly soluble in water and have been detected as contaminants in surface and ground waters in several states. Surveys of wells and drinking waters found that levels rarely exceeded 18 parts per billion (ppb) or 18 $\mu g/L$ (1). In California, wells exceeding this level were closed or their waters were diluted before public use. Assuming a daily water consumption of approximately 2 Liters per person per day, the consumption of water containing up to 16 ppb perchlorate would result in the ingestion 36 μg of perchlorate daily.

The major pharmacological effect of the perchlorate anion

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is to decrease the active transport of iodide into the thyroid. Perchlorate is a competitive inhibitor of the sodium-iodide symporter (NIS), the thyroid cell surface protein responsible for transporting iodide from the plasma into the thyroid. The rat symporter was first cloned by Dai et al. in 1996 (2) and the human NIS by Smanik et al. (3). In view of its antithyroid action, perchlorate was used in large doses up to 2000 mg daily to treat hyperthyroid Graves' disease in the 1950s and early 1960s (4). This practice was abandoned because of a concern for a toxic effect on the bone marrow at high doses that resulted in aplastic anemia and agranulocytosis (5–9). However, in 1984, Wenzel and Lente (10) reported the successful use of perchlorate as therapy of hyperthyroid Graves' disease with daily doses of 900 mg or less for up to 1 year. No serious side effects were reported. Shortly thereafter, perchlorate was also used in doses of up to 1000 mg daily for 4 weeks or longer as adjunctive therapy of iodine-induced hyperthyroidism secondary to the iodine rich antiarrhythmic drug, amiodarone (11). More recently, perchlorate (900 mg daily) has also been reported to be useful in preventing iodine-induced hyperthyroidism following the administration of iodine rich x-ray contrast agents used in coronary angiography (12). In these more recent studies, no serious toxic effects were observed. Perchlorate has also been given to euthyroid volunteers. Burgi et al. (13) reported in 1974 that the daily administration of 600 mg perchlorate to 5 normal volunteers over the course of a week increased nonthyroxine iodine release by 65%, suggesting that iodine uptake might have been completely blocked. In 1992, Brabant et al. (14) treated five healthy males with 900 mg potassium perchlorate daily for 4 weeks and were unable to induce thyroid iodine depletion. Both of these studies were conducted in moderately iodine deficient regions and not in an area where ambient iodine intake is adequate, as in the United States.

We recently studied workers in the only industrial site in the United States currently manufacturing ammonium perchlorate (American Pacific Corporation, Cedar City, UT) and found no adverse effects (15). Airborne exposures ranged from 0.004 to 167 mg total particulate perchlorate daily and urinary perchlorate was readily detected in the exposed workers. The workers were grouped into four exposure categories with mean absorbed perchlorate levels of 0.9, 4, 11, and 34 mg daily. Serum perchlorate ranged from 0 to 1.6 μg/mL. No thyroid abnormalities were found on physical examination and no differences in thyroid function (serum thyrotropin [TSH], free thyroxine index (FTI), total triiodothyronine (TT_3), and thyroid peroxidase (TPO) antibodies) were detected among the four groups of workers, including those in a comparison group with no definable exposure to perchlorate. Finally, neither hematologic nor blood chemistry abnormalities were present in these workers chronically exposed to perchlorate.

The present study was carried out to determine whether the ingestion of perchlorate enriched water (10 mg/d) would affect thyroid function in normal male volunteers. The most sensitive effect of perchlorate is on the thyroid iodine uptake. Therefore, thyroid ^{123}I uptakes (RAIU) before, during, and after perchlorate ingestion were also determined. The daily 10-mg dose of perchlorate is approximately 300 times greater than potential exposure from the consumption of drinking waters known to contain perchlorate. A no-observed-adverse-effect-level (NOAEL) of perchlorate was sought to evaluate potential human health risks from environmental perchlorate contamination.

Materials and Methods

This study was carried out in nine euthyroid male volunteers ages 22 to 30 years after approval by the Institutional Review Board. Subjects were enrolled after a normal complete physical examination that included a thyroid exam. Blood was obtained for baseline measurement of thyroid function tests, TPO antibodies, complete blood count (CBC), and routine chemistries. A spot urine was obtained for routine urinalysis. All baseline tests were normal and the nine volunteers were enrolled in the study. A baseline 24-hour urine was collected, and baseline thyroid RAIUs were measured at 4, 8, and 24 hours after the ingestion of 150 μCi ^{123}I.

Ten milligrams of perchlorate as potassium perchlorate was dissolved in 1-L bottles of spring water. Each subject was asked to consume 1 L/d intermittently during waking hours for 14 days in order to simulate how the general public ordinarily drinks water. Blood specimens were drawn between 8:00 and 9:00 AM, and 24-hour urines were obtained on days 7 and 14 during perchlorate ingestion and again 2 weeks after perchlorate was discontinued. The 4-, 8-, and 24-hour thyroid ^{123}I uptakes were repeated on the final day of perchlorate consumption (exposure day 14) and again 2 weeks later.

CBC and routine blood chemistries were measured on all samples drawn during the course of the study to identify any potential perchlorate-induced abnormalities. Twenty-four–hour urine collections were measured for iodine, perchlorate, and creatinine. Thyroid function tests were measured on blood drawn throughout the study and were measured after completion of the study, in duplicate, in the same assay, and in random order. Serum iodine and perchlorate levels were measured in the blood samples.

CBC and blood chemistries were measured by standard methods at Quest Diagnostics, Cambridge, MA. Thyroid

TABLE 1. THE EFFECT OF PERCHLORATE (ClO_4) ADMINISTRATION (10 mg/d) FOR 14 DAYS ON THYROID FUNCTION TESTS

Time	*T_4 (μg/dL)*	*THBR*	*FTI*	*T_3 (ng/dL)*	*TSH (μU/mL)*
Baseline	6.6 ± 0.4[a]	0.96 ± 0.02	6.3	136 ± 6	1.05 ± 0.14
7 Days ClO_4	6.7 ± 0.4	0.94 ± 0.02	6.2	140 ± 8	1.00 ± 0.17
14 Days ClO_4	6.6 ± 0.5	0.96 ± 0.03	6.3	151 ± 6	0.96 ± 0.12
14 Days after ClO_4	6.5 ± 0.5	0.97 ± 0.02	6.3	157 ± 9	1.23 ± 0.17

[a]Mean ± SE.

T_4 thyroxine; THBR, thyroid hormone binding ratio; FTI, free thyroxine index; T_3 triiodothyronine; TSH, thyrotropin.

TABLE 2. URINE AND SERUM PERCHLORATE (ClO_4) VALUES BEFORE, DURING, AND AFTER THE INGESTION OF 10 mg OF ClO_4 DAILY FOR 14 DAYS

Time	*Urine perchlorate (mg/24 hr)*	*Serum perchlorate (μg/mL)*
Baseline	< 0.5	0
7 Days ClO_4	7.7 ± 0.8[a]	0.61 ± 0.02
14 Days ClO_4	7.5 ± 1.0	0.59 ± 0.02
14 Days after ClO_4	< 0.5	0

[a]Mean ± SE.

function tests were carried out in the Endocrine-Hypertension Research Laboratory of the Brigham & Women's Hospital by the following methods (normal values in parentheses): TSH (0.45 to 4.5 μU/mL) was measured by chemiluminescence (Beckman Access, Chaska, MN); thyroxine (T_4) (5 to 11 μg/dL) by radioimmunoassay (Diagnostic Products Corps, Los Angeles, CA); T_3 (87 to 178 ng/dL) by radioimmunoassay (Beckman Access); and thyroid hormone binding ratio (THBR; 0.85 to 1.10) by ^{125}I-T_3 displacement assay (Diagnostics Products Corps); and TPO (< 20 IU/mL) by enzyme-linked immunosorbent assay (American Laboratory Products Co., Windham, NH) The FTI index is the product of the T_4 concentration and the THBR.

Urinary creatinine and iodine, and serum total iodine measurements were performed using the Jaffe alkaline picrate method for creatinine and the Sandell-Kolthoff reaction for iodine as modified by Benotti et al. (16). Urinary perchlorate measurements were performed at the American Pacific Corporation Laboratory, Cedar City, Utah, using a method with a detection limit of 0.5 parts per million (ppm) or greater (15). Serum perchlorate measurements were carried out at the Operational Toxicology Branch, AFRL, Wright-Patterson, AFB, Ohio with a detection limit of 0.005 μg/ml.

Statistical analysis for the thyroid RAIU values was carried out by analysis of variance (ANOVA) with *post hoc* pairwise comparisons using Tukey's method. The outcome variable was log transformed to achieve greater homoscedasticity and a more Gaussian distribution. Serial analyses were done: a three factor ANOVA with factors patient, treatment, and time and a set of two factor ANOVAs, one for each of the three times. Also, to check that repeated measures among the patients did not affect results, the analogous mixed model ANOVAs were run with the subject as a random effect. Statistical analyses of the thyroid function tests and urine and serum perchlorate and iodine values were carried out by ANOVA and Student Newman Keuls (SNK). Values are reported as the mean ± standard error (SE).

Results

No adverse effects of perchlorate were noted on hepatic, renal, or hematologic parameters. Throughout the study, the volunteers remained asymptomatic and had no changes in their normal physical exams.

Thyroid function tests

Baseline thyroid function tests were normal and remained unchanged during and after perchlorate administration (Table 1). TPO-antibodies were negative in all subjects.

Urine and serum perchlorate levels

Eighteen samples of the perchlorate drinking water were analyzed for perchlorate content and found to contain 10.8 ± 0.6 mg/L bottle, which was almost identical to the amount of perchlorate added to the bottles (Table 2). No perchlorate was detected in the urine samples collected before perchlorate exposure or 2 weeks after perchlorate had been discontinued. During perchlorate administration, urinary perchlorate markedly increased, reaching levels of 7.7 ± 0.8 mg per 24 hours and 7.5 ± 1.0 mg per 24 hours at 7 and 14 days, respectively. Perchlorate was not detected in the serum before and 2 weeks after perchlorate ingestion. During perchlorate administration, serum levels were markedly elevated to 0.61 ± 0.02 and 0.59 ± 0.02 μg/mL on days 7 and 14, respectively.

Urine and serum iodine levels

There were no significant changes in urinary iodine excretion during or 2 weeks after perchlorate administration whether values were expressed as micrograms per deciliter, micrograms per total volume, or micrograms per gram of creatinine. Values were variable throughout the study as iodide ingestion was not controlled in the volunteers' diet (Table 3). Serum total iodine values remained normal and unchanged during and 2 weeks after perchlorate ingestion.

TABLE 3. URINE AND SERUM IODINE VALUES BEFORE, DURING, AND AFTER THE INGESTION OF 10 mg ClO_4 DAILY FOR 14 DAYS

Time	*Urine Iodine (μg/24 hr)*	*Serum iodine (μg/dL)*
Baseline	254 ± 69	6.5 ± 0.42[a]
7 Days ClO_4	233 ± 49	6.2 ± 0.34
14 Days ClO_4	385 ± 123	6.4 ± 0.37
14 Days after ClO_4	208 ± 42	6.3 ± 0.57

[a]Mean ± SE.

TABLE 4. THYROID[123] I UPTAKES BEFORE, DURING, AND AFTER THE INGESTION OF 10 mg ClO_4 DAILY FOR 14 DAYS

	Thyroid ^{123}I Uptake (% dose)		
Time	*Baseline*	*14 Days on ClO_4*	*14 Days after ClO_4*
4 Hours	12.5 ± 1.3	8.2 ± 0.7[a]	16.6 ± 2.4[b]
8 Hours	17.3 ± 1.9	10.6 ± 1.0[a]	21.9 ± 2.8[b]
24 Hours	23.6 ± 2.6	14.0 ± 1.6[a]	27.1 ± 3.3[c]

[a] $p < 0.01$ vs. baseline and after ClO_4
[b] $p < 0.01$ vs. baseline.
[c] $p < 0.05$ vs. baseline.

Thyroid ^{123}I uptakes

Baseline 4-, 8-, and 24-hour thyroid RAIUs were normal (Table 4 and Fig. 1). During perchlorate ingestion, there was a highly significant decrease in the thyroid RAIUs at all three time points. The average decrease below baseline values over all three time points was 38%. Two weeks after perchlorate was discontinued, the thyroid RAIUs were significantly higher than baseline at 4, 8, and 24 hours, averaging 125% of baseline values.

Discussion

The present study demonstrates that low doses of perchlorate (10 mg/d) administered for 14 days did not affect circulating thyroid hormone and TSH concentrations but did significantly decrease the thyroid ^{123}I uptake. This finding was not unexpected because the major effect, and almost certainly the only effect, of perchlorate on the thyroid is a decrease in the thyroid iodide trap by competitive inhibition of NIS (2). Because the thyroid has large stores of iodine, T_4, and T_3, the observed decrease in the thyroid iodide trap would not be expected to have resulted in changes in the circulating levels of thyroid hormones and TSH over a 2-week period. This modest reduction in the thyroid RAIU would have decreasd the amount of stable iodide entering the thyroid in these subjects but dietary iodine was more than adequate (approximately 250 μg/d) and over 2 weeks this modest decrease would not have significantly affected the amount of stored hormones and their subsequent release. Individuals with Hashimoto's thyroiditis and those residing in areas of iodine deficiency might be more sensitive to the effects of perchlorate because they may have decreased thyroid iodine stores. It is likely that the observed effect on the thyroid RAIU is physiological because a rebound increase in the RAIU was observed after perchlorate was discontinued, which may represent an increase in NIS. This rebound increase in the thyroid RAIU is almost identical to the increase reported by Stanbury and Wyngaarden (17) in hyperthyroid patients receiving therapeutic doses of perchlorate. In our previous study of workers in the plant that produced perchlorate, exposure to much higher levels of perchlorate for months and years did not affect thyroid function tests or cause clinical thyroid disease (15). However, thyroid RAIUs could not be measured in these workers.

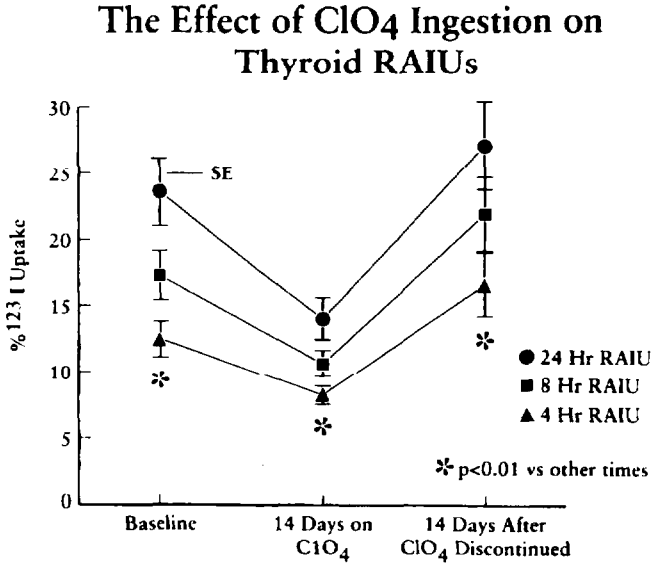

FIG. 1. The effect of low-dose perchlorate on the 4-, 8-, and 24-hour thyroid ^{123}I uptakes.

Serum perchlorate levels were consistently elevated and varied only slightly among the nine volunteers. The serum levels were essentially equal at the end of the first and second week of ingestion. There was considerable variation in urinary perchlorate values between individuals and between the two collections from each subject. This is most likely due to incomplete 24-hour urine collections and different patterns of perchlorate ingestion in relation to the urine collections. For instance, 24-hour urine perchlorate values in four subjects demonstrated approximately 100% of the ingested amount while three subjects excreted approximately 50% of the ingested perchlorate. Because serum perchlorate values were consistent in all subjects, as noted above, incomplete urine collections is a more plausible explanation than incomplete perchlorate ingestion.

Perchlorate readily crosses the placenta and could pose a potential hazard to the fetus by decreasing fetal thyroid iodine stores and subsequent thyroid function. However, this possibility is unlikely because a recent report from regions of perchlorate-contaminated ground water, with levels as high as 16 μg/L, found no evidence of an increased incidence of congenital hypothyroidism (18).

It seems unlikely that the low levels of perchlorate detected in surface and ground waters pose a risk to the general population because no effect on thyroid function was observed in perchlorate plant workers exposed for months and years to as much as 34 mg of perchlorate daily (15). Although a decrease in the thyroid RAIU was observed with no change in circulating hormones in the present study with

2 weeks of a low dose of ClO_4, it is not known whether continuous exposure to low levels of ClO_4 over a prolonged period of time would perturb thyroid function. A longer study period of 6 months using low doses of perchlorate is currently being undertaken to address this concern. In addition, it would be of interest to establish a NOAEL of ClO_4 on the thyroid RAIU.

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References

1. Office of Ground Water and Drinking Water. Perchlorate. Washington, D.C: Environmental Protection Agency; December 15, 1998.
2. Dai G, Levy O, Carrasco N 1996 Cloning and characterization of the thyroid iodide transporter. Nature **379**:458–460.
3. Smanik PA, Liu Q, Furminger TL, Ryu K, Xing S, Mazzaferri EL, Jhiang SM 1996 Cloning of the human sodium lodide symporter. Biochem Biophys Res Commun **226**:339–345.
4. Wolff J 1998 Perchlorate and the thyroid gland. Pharmacol Rev **50**:89–105.
5. Hobson QJ 1961 Aplastic anaemia due to treatment with potassium perchlorate. BMJ **1**:1368–1369.
6. Johnson SR, Moore WC 1961 Fatal aplastic anaemia after treatment of thyrotoxicosis with potassium perchlorate. BMJ **1**:1369–1371.
7. Fawcett JW, Clarke CW 1961 Aplastic anaemia due to potassium perchlorate. BMJ **1**:1537.
8. Krevans JR, Asper SP, Rienhoff WF 1962 Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. JAMA **181**:162–164.
9. Barzilai D, Sheinfeld M 1966 Fatal complications following use of potassium perchlorate in thyrotoxicosis: Report of two cases and a review of the literature. Israel J Med Sci **2**:453–456.
10. Wenzel KW, Lente JR 1984 Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: Evidence against an immunosuppressive action of thionamide drugs. J Clin Endocrinol Metab **58**:62–69.
11. Martino E, Aghini-Lombardi F, Mariotti S, Baschieri L, Lenziardi M, Safran M, Braverman E, Pinchera A 1986 Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. J Endocrinol Invest **9**:201–207.
12. Nolte W, Muller R, Siggelkow H, Emrich D, Hufner M 1996 Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study. Eur J Endocrinol **134**:337–341.
13. Burgi H, Benguerel M, Knopp J, Kohler H and Studer H 1974. Influence of perchlorate on the secretion of non-thyroxine iodine by the normal human thyroid gland. Eur J Clin Invest **4**:65–69.
14. Brabant G, Bergmann P, Kirsch CM, Kohrle J, Hesch RD, von zur Muhlen A 1992 Early adaptation of thyrotropin and thyroglobulin secretion to experimentally decreased iodine supply in man. Metabolism **41**:1093–1096.
15. Lamm SH, Braverman LE, Li FX, Richman K, Pino S, Howearth G 1999 Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. JOEM **41**:248–260.
16. Benotti J, Benotti N, Pino S, Gardyna H 1965 Determination of total iodine in urine, stools, diets, and tissue. Clin Chem **11**:932–936.
17. Stanbury JB, Wyngaarden JB 1952 Effect of perchlorate on the human thyroid gland. Metabolism **1**:533–539.
18. Lamm SH, Doemland M 1999 Has perchlorate in drinking water increased the rate of congenital hypothyroidism? JOEM **41**:409–411.

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